L9 ANSWER 7 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1999:99102 BIOSIS

DOCUMENT NUMBER: PREV199900099102

TITLE: Inhibition of cell cycle progression by **rapamycin** induces **T** cell clonal **anergy** even in the presence of costimulation.

AUTHOR(S): Powell, J. D.; Lerner, C. G.; Schwartz, R. H.

CORPORATE SOURCE: LCMI, NIAID, NIH, Bethesda, MD USA

SOURCE: Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 21A.
Meeting Info.: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998 The American Society of Heamatology
. ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

L9 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:300458 CAPLUS
DOCUMENT NUMBER: 128:320568
TITLE: Methods and materials for the induction of **T** cell **anergy**
INVENTOR(S): De Boer, Mark; Conroy, Leah B.
PATENT ASSIGNEE(S): Chiron Corp., USA
SOURCE: U.S., 35 pp., Cont.-in-part of U.S. Ser. No. 15,147.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5747034	A	19980505	US 1994-200716	19940218
US 5397703	A	19950314	US 1992-910222	19920709
US 5869050	A	19990209	US 1993-15147	19930209
CA 2183680	AA	19950824	CA 1995-2183680	19950119
WO 9522619	A1	19950824	WO 1995-US897	19950119
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9516877	A1	19950904	AU 1995-16877	19950119
EP 745136	A1	19961204	EP 1995-908634	19950119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09510607	T2	19971028	JP 1995-521804	19950119

PRIORITY APPLN. INFO.:
US 1992-910222 A2 19920709
US 1993-15147 A2 19930209
US 1994-200716 A 19940218
WO 1995-US897 W 19950119

AB Anti-B7-1 antibodies or other B7-1 ligands may be used to prevent or treat a T-cell-mediated immune system disease in a patient or to induce antigen-specific tolerance. The anti-B7-1 antibodies may be used to cause **T** cell **anergy**, treat allograft transplant rejection, treat graft vs. host disease, and prevent or treat rheumatoid arthritis. An immunosuppressive agent is co-administered with the antibody.

L9 ANSWER 5 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999172213 MEDLINE
DOCUMENT NUMBER: 99172213 PubMed ID: 10072524
TITLE: Inhibition of cell cycle progression by **rapamycin** induces **T** cell clonal **anergy** even in the presence of costimulation.
AUTHOR: Powell J D; Lerner C G; Schwartz R H
CORPORATE SOURCE: Laboratory of Cellular and Molecular Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Mar 1) 162 (5) 2775-84. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990414

AB Costimulation (signal 2) has been proposed to inhibit the induction of **T** cell clonal **anergy** by either directly antagonizing negative signals arising from TCR engagement (signal 1) or by synergizing with signal 1 to produce IL-2, which in turn leads to proliferation and dilution of negative regulatory factors. To better define the cellular events that lead to the induction of anergy, we used the immunosuppressive agent **rapamycin**, which blocks T cell proliferation in late G1 phase but does not affect costimulation-dependent IL-2 production. Our data demonstrate that full T cell activation (signal 1 plus 2) in the presence of **rapamycin** results in profound **T** cell **anergy**, despite the fact that these cells produce copious amounts of IL-2. Similar to conventional anergy (induction by signal 1 alone), the **rapamycin**-induced anergic cells show a decrease in mitogen-activated protein kinase activation, and these cells can be rescued by culture in IL-2. Interestingly, the **rapamycin**-induced anergic cells display a more profound block in IL-3 and IFN-gamma production upon rechallenge. Finally, in contrast to **rapamycin**, full T cell activation in the presence of hydroxyurea (which inhibits the cell cycle in early S phase) did not result in anergy. These data suggest that it is neither the direct effect of costimulation nor the subsequent T cell proliferation that prevents anergy induction, but rather the biochemical events that occur upon progression through the cell cycle from G1 into S phase.

L9 ANSWER 3 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:312008 BIOSIS
DOCUMENT NUMBER: PREV200100312008
TITLE: **Rapamycin** induces long term bone marrow chimerism in the absence of long term immunosuppression in mismatched stem cell transplantation; application to sickle cell mice.
AUTHOR(S): Powell, J. D. (1); Fitzhugh, C. A.; Kang, E. M.; Weiss, S.; Schwartz, R. H. (1); Tisdale, J. F.
CORPORATE SOURCE: (1) NIAID, NIH, Bethesda, MD USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 580a-581a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Engagement of the TCR leads to not only T cell activation but also upregulation of negative regulatory factors which promote tolerance. We have previously demonstrated that in contrast to cyclosporine (CSA) which inhibits anergy induction, **rapamycin** (Rapa) can promote **T** cell **anergy** even in the presence of costimulation. As such, we sought to determine if Rapa could be utilized to promote bone marrow chimerism in a F1 into parent transplantation model using minimal conditioning. Splenocytes (100 X 106) from G-CSF mobilized (C57BL/6 X BALB/C)F1 mice were injected into C57BL/6 recipients which had received 300cGy conditioning and either no immunosuppression (No IS, n=5), CSA (20mg/kg/d, n=6) I.P., or Rapa (3mg/kg/d, n=7) I.P. for 28 days. The No IS mice rejected their grafts by 1 week, while the CSA mice initially demonstrated donor-chimerism (10-15%) but eventually rejected their grafts. In contrast, the Rapa mice demonstrated progressively increasing donor chimerism which plateaued at 60-80%. More importantly, the Rapa mice have remained chimeric at this level for >3 months after stopping immunosuppression. Donor chimerism was preserved among CD4+, CD8+, B cell and granulocyte compartments. Donor cells were also detected in the thymuses of chimeric mice indicating a potential role for thymic deletion.

In MLRs, splenocytes from both the No IS and CSA mice responded to BALB/c stimulator cells while cells from the Rapa mice were unresponsive. Using the Rapa protocol, mice thalassemic for murine Hb and transgenic for human HbS (expressing 60% human HbS) were transplanted with stem cells from normal F1 mice. Donor myeloid chimerism as low as 30% resulted in undetectable levels of HbS by Hb electrophoresis. Whether the virtually undetectable levels of HbS in the transplanted mice reflects a survival advantage of the normal RBC's or an advantage at the level of erythropoeisis is currently being investigated. In in vitro functional assays, blood from transplanted HbS trait mice displayed decreased turbidity in the sickle prep test as well as decreased or absent sickling on Sodium Bisulfite prepared smears compared to nontransplant controls. Current experiments to further characterize the rheologic properties of

chimeric mice as well as pathology in transplanted homozygous sickle mice are underway. Finally, these data suggest that this simple, non toxic, pharmacologic protocol might be useful in attaining hematopoietic chimerism in human allogeneic stem cell transplantation.

L9 ANSWER 2 OF 11 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2001106121 MEDLINE
DOCUMENT NUMBER: 20571934 PubMed ID: 11123330
TITLE: Relative resistance in the development of **T** cell **anergy** in CD4+ T cells from simian immunodeficiency virus disease-resistant sooty mangabeys.
AUTHOR: Bostik P; Mayne A E; Villinger F; Greenberg K P; Powell J D; Ansari A A
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322, USA.. pbostik@emory.edu
CONTRACT NUMBER: RO1 AI27057 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 Jan 1) 166 (1) 506-16. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB Despite high viral loads, T cells from sooty mangabey (SM) monkeys that are naturally infected with SIV but remain clinically asymptomatic, proliferate and demonstrate normal Ag-specific memory recall CD4(+) T cell responses. In contrast, CD4(+) T cells from rhesus macaques (RM) experimentally infected with SIV lose Ag-specific memory recall responses and develop immunological anergy. To elucidate the mechanisms for these distinct outcomes of lentiviral infection, highly enriched alloreactive CD4(+) T cells from humans, RM, and SM were anergized by TCR-only stimulation (signal 1 alone) and subsequently challenged with anti-CD3/anti-CD28 Abs (signals 1 + 2). Whereas alloreactive CD4(+)T cells from humans and RM became anergized, surprisingly, CD4(+) T cells from SM showed marked proliferation and IL-2 synthesis after restimulation. This resistance to undergo anergy was not secondary to a global deficiency in anergy induction of CD4(+) T cells from SM since incubation of CD4(+) T cells with anti-CD3 alone in the presence of **rapamycin** readily induced anergy in these cells. The resistance to undergo anergy was reasoned to be due to the ability of CD4(+) T cells from SM to synthesize IL-2 when incubated with anti-CD3 alone. Analysis of phosphorylated kinases involved in T cell activation showed that the activation of CD4(+) T cells by signal 1 in SM elicited a pattern of response that required both signals 1 + 2 in humans and RM. This function of CD4(+) T cells from SM may contribute to the resistance of this species to SIV-induced disease.

L82 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 2000000825 PCTFULL ED 20020515
TITLE (ENGLISH): DETECTION AND MODULATION OF CELLULAR IMMUNITY TO IMMUNE
PRIVILEGED ANTIGENS
TITLE (FRENCH): PROCEDE ET AGENTS POUR LA DETECTION ET LA MODULATION D'IMMUNITE CELLULAIRE SUR DES ANTIGENES PRIVILEGIES IMMUNS
INVENTOR(S): DARNELL, Robert, B.; ALBERT, Matthew, L.; BHARDWAJ, Nina
PATENT ASSIGNEE(S): THE ROCKEFELLER UNIVERSITY
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000000825	A2	20000106

DESIGNATED STATES: AU CA JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.:	WO 1999-US14827 A	19990630
PRIORITY INFO.:	US 1998-09/107,978	19980630
	US 1999-09/107,978	19990629

DETD In the practice of the above method, certain immune-privileged antigens may not be adequately
taken up by **dendritic** cells for presentation on the cell surface, nor will exposure of the deDdritic cells to the intact antigen or its peptides. . . be readily processed and presented. Among various known means for increasing antigen presentation by poorly immunogenic or poorly processed antigens, use of **apoptotic cells** expressing the desired antigen to deliver antigen to dendritic cells (17), in addition to other known means such as the use of. . .